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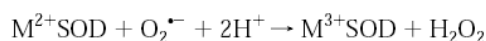
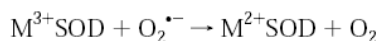
*Chapter 10***FUNCTIONAL AND STRUCTURAL MIMICS OF
SUPEROXIDE DISMUTASE ENZYMES*****István Pálinkó****Department of Organic Chemistry, University of Szeged,
Dóm tér 8, Szeged, H-6720 Hungary**ABSTRACT**

Superoxide dismutase (SOD) enzymes form important defence line in living organisms. Through a dismutation reaction they transform the highly reactive superoxide radical ion to oxygen and hydrogen peroxide. The latter compound is further transformed by catalase or peroxidase enzymes to water and oxygen. The overall structure of the enzymes and those of the active sites are largely known, thus, it has been revealed that in eukaryotes Cu(II) and Zn(II) ions act as cofactors and they are connected with an imidazolate bridge and this structural unit is coordinated with amino acids. In prokaryotes the SOD enzymes contain Mn(II) or Fe(II) or Ni(II) in their active centres. In order to learn about the working mechanism of SOD enzymes at the molecular level various structural mimics were prepared and their structural transformations during the dismutation reaction was followed. Gathering adequate amount of information allowed the preparation of functional mimics that are not necessarily copies of the active sites of the enzymes, nevertheless, display considerable SOD activity. Both functional and structural mimics are comprehensively dealt with in this review. Although enzymes may seem to be attractive catalysts for promoting real-life reactions effectively with high selectivity, they can seldom if ever be used under industrial conditions, i.e. at high temperatures and pressures. The SOD enzymes for promoting oxygen transfer reactions are not durable enough under these conditions either. The complexes mimicking SOD activities perform better in this respect, however, their reusabilities are limited, because of separation problems. A solution can be the immobilisation of these SOD mimicking complexes on solid or semi-solid supports. Even if the activity is not better than the support-free complexes, the catalyst can be filtered at the end of the reaction and can easily be recycled. Attempts for immobilisation are also comprehensively reviewed and immobilised complexes with surprisingly high SOD activities are reported as well. Full

characterisation of these materials is given and rationalisation of their exceptionally high activities is offered.

SUPEROXIDE DISMUTASE (SOD) ENZYMES: TYPES, ACTIVE CENTRES, MECHANISMS OF SUPEROXIDE DISMUTATION

Organisms exposed to molecular oxygen obviously encounter reactive oxygen species that are formed by the reduction of O_2 by oxidoreductases [1]. These species include superoxide, $O_2^{\bullet-}$, the one-electron-reduced product of dioxygen. High superoxide levels have been detected in a number of disorders like diabetes [2], cell death and tissue damage that occurs following a stroke or heart attack [3], some neurodegenerative diseases [4-7] and some types of cancer are thought to arise from mutations induced by $O_2^{\bullet-}$ damage to DNA [8,9]. Organisms have developed two known defences for the reduction and/or oxidation of superoxide: the superoxide dismutase (SOD) and the superoxide reductase (SOR) enzymes [10–16]. The classical SOD enzymes disproportionate superoxide to hydrogen peroxide and dioxygen and at the end of the cycle the metal ion reduced in the first step is oxidised once again (it is often called to ping-pong mechanism) [13,14,17].



SOR enzymes selectively reduce superoxide to hydrogen peroxide in anaerobic organisms without the formation of oxygen as a by-product.

Types of SOD Enzymes and the Structure of the Active Centres

In the immediate followings only some structural aspects of the various SOD enzymes and their consequences are discussed briefly, and later on SOD-related modelling studies will be discussed.

To date, four types of SOD enzymes have been identified in various living organisms: Cu,ZnSOD is found in all eukaryotic species and is also widely distributed in prokaryotes [18]; MnSOD is present in many bacteria, mitochondria, and chloroplasts, as well as in the cytosol of eukaryotic cells [19]; FeSOD is found in bacteria and several higher plants [20,21]; NiSOD enzymes are identified in several bacteria of the *Streptomyces* genera and several *Actinomycetes* [22].

Reduced FeSOD enzymes contain a nonheme iron as a five-coordinated active site ligated by three histidine units, an aspartate group, and a H_2O/OH^- ligand ($pK_a = 8.5$) supported by a conserved H-bonding network. FeSODs and MnSODs are homologous, the coordination environment at the metallic centres are the same in both enzymes (Figure 1).

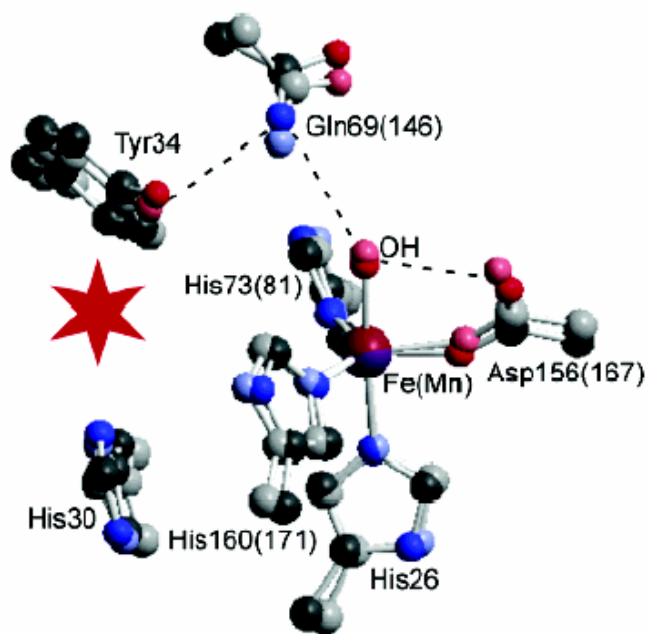


Figure 1. Overlay of active-site models of Fe(III)SOD (dark) and Mn(III)SOD (light) enzymes based on PDB files 1ISB and 1VEW, respectively. The numbering schemes relate to *E. coli* FeSOD and, in parentheses, MnSOD if different. The putative substrate prebinding site of FeSOD is indicated by an asterisk (*). Reprinted with permission from Ref. [14], Jackson, T.A.; Brunold, T.C. *Acc. Chem. Res.* 2004, 37, 461–470. Copyright © American Chemical Society.

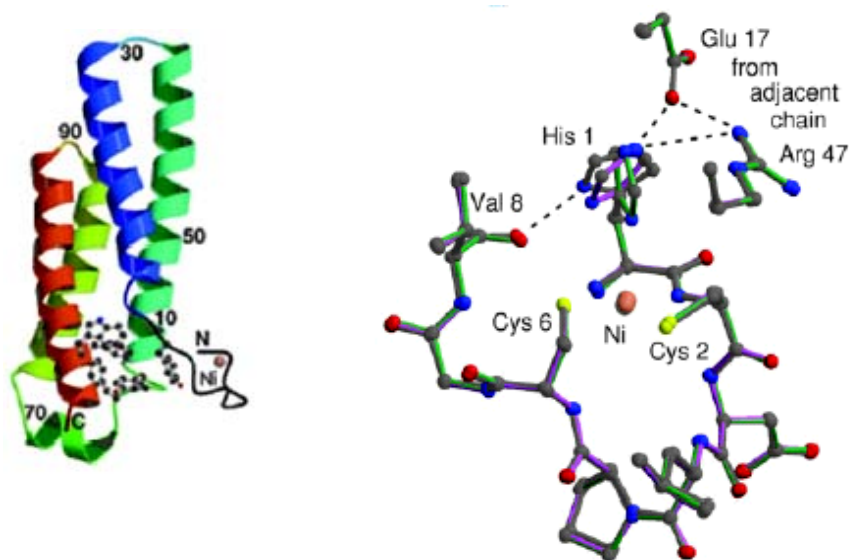


Figure 2. The NiSOD enzyme and its active centre. Reprinted with permission from Ref. [22], Wuerges, J.; Lee, J.-W.; Yim, Y.-I.; Yim, H.-S.; Kang, S.O.; Carugo, K.D. *Proc. Natl. Acad. Sci. USA* 2004, 101, 8569–8574. Copyright © National Academy of Sciences USA.

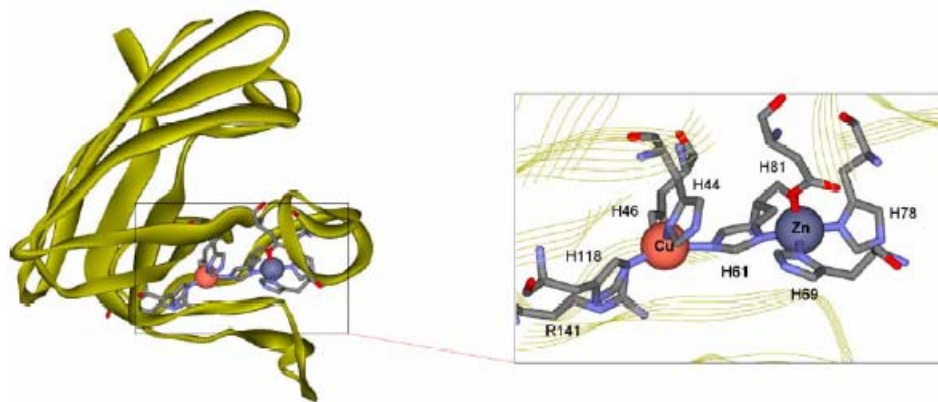


Figure 3. The CuZnSOD enzyme and its active centre based on refs. [23-25].

The NiSOD enzyme is a homohexamer consisting of four-helix-bundle subunits. The catalytic centre resides in the terminal active-site loop, where the Ni(III) ion is coordinated by the amino group of histidine-1, the amide group of cysteine-2, two thiolate groups of cysteine-2 and cysteine-6, and the imidazolate nitrogen of histidine-1 as an axial ligand, which is lost in the chemically reduced state [22] (Figure 2).

The coordination environment of the active site in the CuZnSOD enzymes is different again [23-25]. The cofactor involved directly in the catalytic cycle is the Cu(II) ion [this is the oxidised, while the Cu(I) ion is the reduced state]. The Zn(II) is not involved directly in the catalytic action, its role is keeping the structure of the active site and restoring it at the end of the catalytic cycle. The coordination environment around the Cu(II) ion is square pyramidal having four histidine molecules in the (nearly) equatorial plane coordinating to the copper ion through one of their imidazole nitrogens. The fifth position is filled by a weakly bound water molecule. One of the histidine molecules is bound to the Zn(II) ion through its other imidazole nitrogen (the nitrogen is deprotonated). Beside the imidazolate bridge the zinc(II) ion is bonded to an aspartic acid and two histidine molecules. The arrangement is depicted in Figure 3.

Mechanistic Features

Although the active site structures of these SOD enzyme types are very different, the main features of their working mechanisms are very similar. The so-called ping-pong mechanism involves $O_2^{\cdot -}$ oxidation at the oxidised form of the catalytically active metal ion followed by proton-induced $O_2^{\cdot -}$ reduction at the reduced form [13,14,17]. By poising the SOD redox potential about half-way between the potentials at which superoxide is oxidized and reduced, the redox active metal centre of SOD is able to both oxidise and reduce the superoxide radical anion depending on the protonation states of the nearby residues and the oxidation state of the metal. The SOD catalytic cycle does not require an external source of electrons. The redox potentials of the SOD metal ion couples are pH-dependent, therefore, the catalytic cycle may be driven through changing the available proton concentration [14,26,27]. The active sites of SOD enzymes are buried within the protein, which makes it easier to

control proton delivery. Details, however, are different. Models do exist for the Cu,ZnSOD as well as the Fe(Mn)SOD enzymes.

The molecular mechanisms that have been developed for the Cu,ZnSOD [23,28], MnSOD and FeSOD enzymes [28,29] are depicted in Figures 4 and 5, respectively.

It is thought that the superoxide anion must bind to the Cu(II) centre, displacing the axial water for electron transfer. This binding is assisted by a positive arginine residue at about 5 Å from the Cu(II) atom and by the weak binding of the axial water ligand. Electron transfer results in loss of oxygen and creates a Cu(I) centre that is three-coordinated and the protonated imidazolate binds only to the zinc ion. A second superoxide anion would then bind to the open coordination position on Cu(I), followed by inner-sphere electron transfer to generate peroxide which is protonated by re-forming the imidazolate bridge. Additional protonation would lead to rapid loss of H₂O₂ and further turnover. It is to be noted that there are problems with this mechanism in terms of breaking and forming the imidazolate bridge; the turnover rate is too high under saturating superoxide conditions, and, if the zinc ion is removed, there is still dismutation with only a limited reduction in the turnover rate.

The mechanism for the manganese and iron containing enzymes is similar to that of Cu,ZnSOD. The major difference is that water binds as hydroxide anion to the oxidized site and thus would not be displaced by superoxide anion; instead, the superoxide anion binds to increase the coordination number of the metal. Reduction then leads to protonation of the bound hydroxide anion to form water, which upon oxidation by a second superoxide anion transfers its proton to the resulting peroxide anion.

Both mechanisms have problems. Attempts for solving them have been made [30,31] and probably, there is still room for improvement. Furthermore, mechanistic concept concerning how the NiSOD enzyme works does not exist.

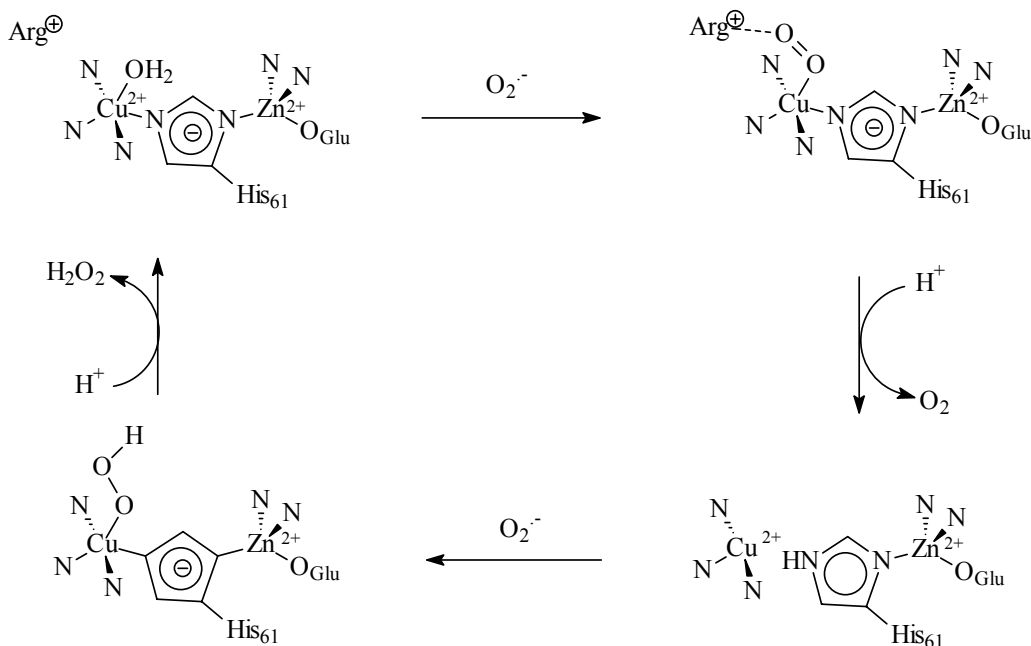


Figure 4. The mechanism of superoxide dismutation by the Cu,ZnSOD enzyme.

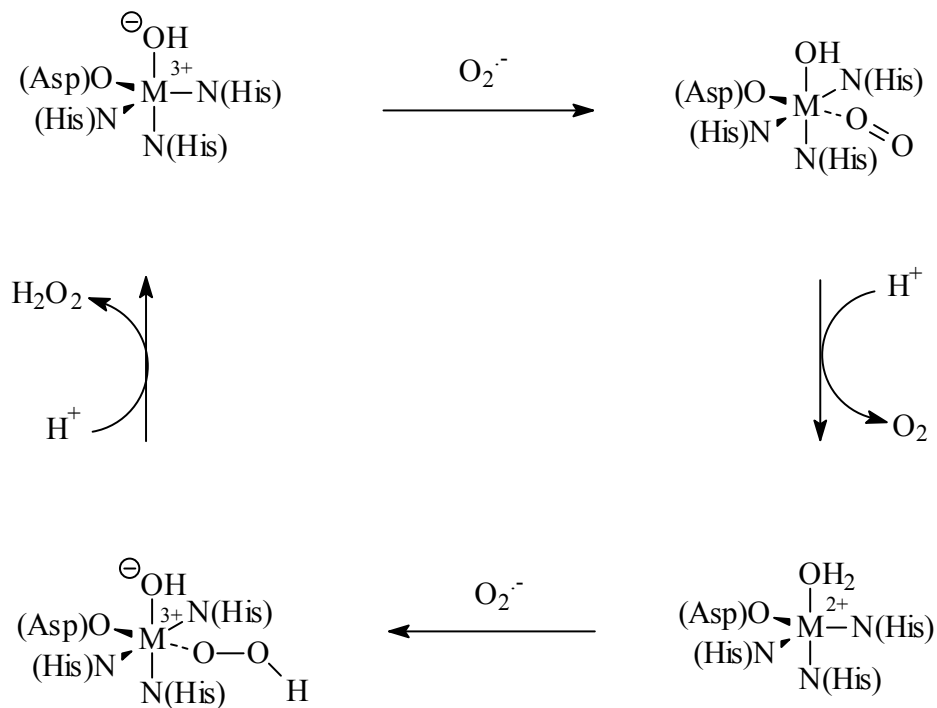


Figure 5. The mechanism of superoxide dismutation by the FeSOD or the MnSOD enzymes.

WHY PREPARE AND STUDY MODELS FOR ACTIVE SITES?

Although much has been learnt about the structures of the various SOD enzymes in general and their active sites in particular, furthermore, main features of their working mechanisms are known, elaborating on missing mechanisms and refining the existing ones are still required. This type of research is greatly helped by skilfully chosen model systems, structurally and functionally mimicking at least the active sites but even better if their environments can be included as well.

Even though natural SOD enzymes catalyse the removal of the harmful superoxide ion from living systems and in preclinical and clinical trials they have shown promising therapeutic properties, they suffer as drug candidates primarily from immunogenic response. This gives impetus to develop new types of free-radical inhibiting enzyme mimetics to be used as pharmaceuticals. Stable low molecular weight metal complexes that can react with superoxide anion and efficiently replicate the activity of the native SOD enzyme have the potential to become a new generation of drugs for the treatment of diseases of various aetiologies.

On the other hand, there is tremendous interest in finding and developing novel catalytic systems (homogeneous or heterogeneous) with high activities and even more importantly, with high selectivities. There are no more selective catalysts than enzymes, therefore copying or mimicking their active centres, i.e. stealing Nature's ideas, may be a promising approach in achieving these goals. Structural mimicking may lead to immediate results, however, it is not always easy, or it does not always lead to durable catalytic materials or it may not be

economically feasible. Fortunately, it is occasionally possible to mimic the active sites functionally, i.e. applying similar but cheaper or to harsher conditions less sensitive ligands without serious loss in activities and selectivities. In order to do it in a sensible way one should learn about the minimum structural requirements for keeping the advantageous features of the enzymes and then look for suitable ligands. This approach requires the synthesis of various models and checking whether they are good functional models or not. Of course, full structural characterisation is also of utmost importance. From the industrial point of view heterogeneous catalysts are preferred to the homogeneous ones, because work-up procedures are more convenient, the catalysts may be easily recovered, regenerated and recycled. In order to meet this requirement the model materials are more and more often immobilised, and there is a tendency to choose supports that mimic the proteomic skeleton as well, hoping that the flexible support may be of help in achieving a conformational environment for the active site modelling moieties, similarly to as it happens in the enzymes.

SOD enzyme mimicking substances may be used in oxygen/electron transfer reactions, thus, they may find application at the bench of synthetic chemists and/or e.g., in fine chemical industry. Good structural and/or functional models, which are metal complexes with one or more central ions, were and are still prepared and some of them were immobilised on rigid as well as flexible supports (vide infra).

SUPPORT-FREE COMPLEXES MIMICKING THE ACTIVE SITES OF SOD ENZYMES

In this section homogeneous complexes displaying SOD activities is described. Published data are overviewed by SOD enzyme types. Within a type the structural model complexes are discussed (the ligands are amino acids or peptides) first, then, the functional models follow.

FeSOD and MnSOD Enzyme Mimics

Structural Mimics

Surprisingly, only one experimental structural modelling study could be located concerning the active site of the MnSOD and none that of the FeSOD enzymes. There are stand-alone theoretical/computational works [32-34] and papers containing molecular modelling sections accompanying experimental work with the enzymes of the wild types [35-39] or mutants [36,40]. All these studies deal with the refinement of the enzymatic dismutation reaction mechanism (elementary reaction steps, redox potentials, product inhibition of the active site, etc.). The experimental work concerns the synthesis and structural characterisation of a Mn(II)–bacitracin complex (for the structure of bacitracin, see Figure 6). That part of the complex resembling the active site in the Mn(II)SOD enzyme is seen in Figure 7.

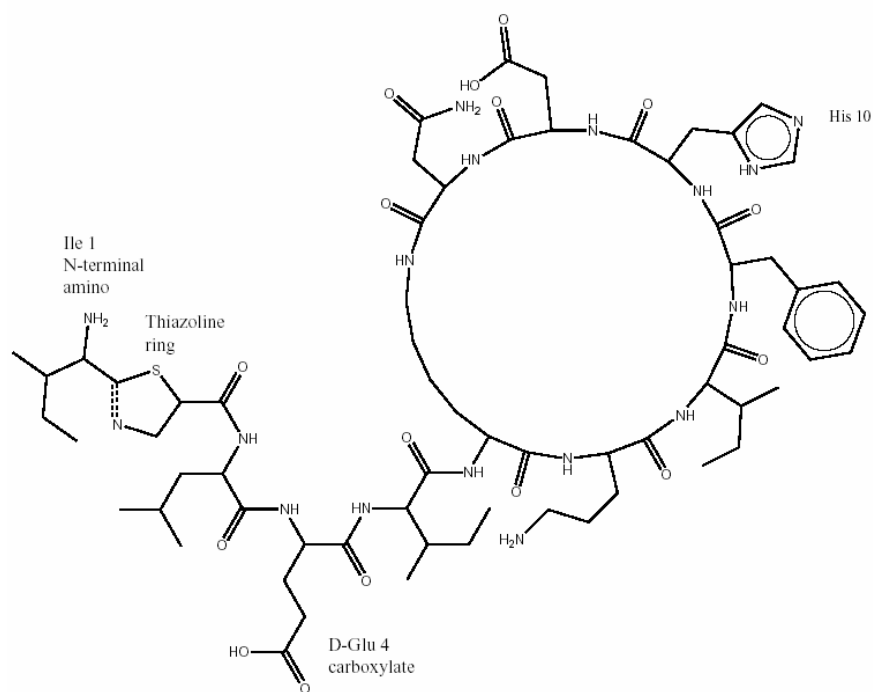


Figure 6. The chemical structure of bacitracin A (PubChem, Accession code CID 439542).

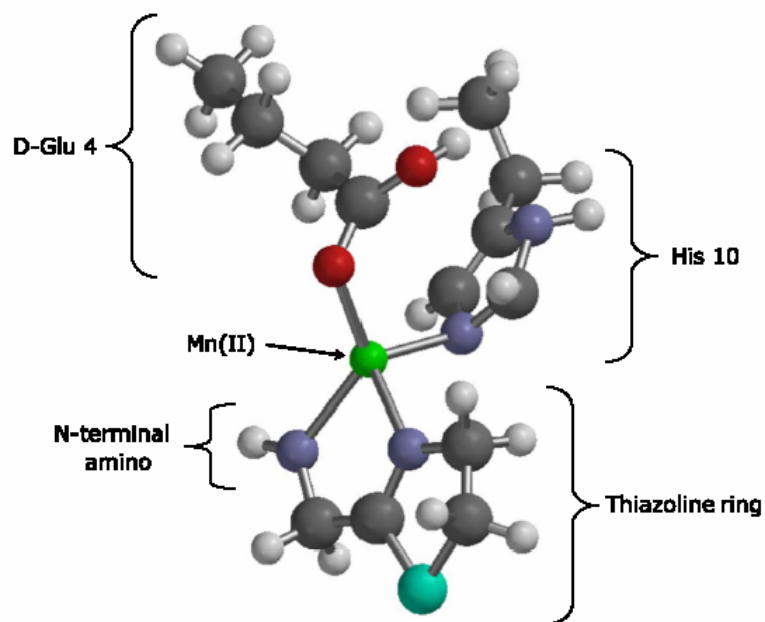


Figure 7. Structure of the Mn(II)–ligand models derived from metallobacitracin complexes. Reprinted with permission from Ref. [41], Piacham, T.; Isarankura-Na-Ayudhya, C.; Nantasenamat, C.; Yainoy, S.; Ye, L.; Bülow, L.; Prachayasittikul, V. *Biochem. Biophys. Res. Commun.* 2006, 341, 925–930. Copyright @Elsevier.

Functional Mimics

Many Mn and Fe complexes have been prepared displaying appreciable SOD activities. The ligands applied can be classified in the following major groups as reviewed some time ago [42], (i) salicyldialdehyde ethylenediimine (salen), (ii) porphyrin and (iii) (1,4,7,10,13-pentaazacyclopenta-decane) derivatives. The Mn(II) complexes of the last ligand group are the most efficient synthetic SOD catalysts known to date (see [43] for relevant citations), and these complexes were the first enzyme mimetics tested in humans. It has been postulated that in these macrocyclic Mn(II) mimetics the profound conformational rearrangements of the macrocyclic pentadentates facilitate subsequent electron transfer and the ligands with high conformational mobility may assist SOD activity [44,45]. Salen ligands could be coordinated to manganese ions, while either manganese or iron ions can be the central ions with the other ligand types. Complexes representative to each ligand class are displayed in Figure 8.

The review [42] lists other complexes of Mn(II) that have been reported to possess modest catalytic SOD activity as monitored by the indirect assay methods. These include the Mn(II)(HL)₂ complex [$H_2L = 2,6\text{-bis(benzamidazol-2-yl)pyridine}$], Mn(II) saccharinate [$MnII(Sac)_2(H_2O)_4$] (the central metal can also be Fe, Co, Ni, Cu or Zn) and Mn(III)bis(2,6-pyridinedicarboxylate) complexes. As far as iron complexes with non-macrocyclic polydentate ligands are concerned aminopolycarboxylate complexes of iron(III) (such as EDTA, NTA, etc.), an iron(II)-containing pigment (neopurpuratin) containing Fe(II) associated with the D-pyridine ligand, a number of Fe(III) complexes with tripodal ligands favouring trigonal-bipyramidal coordination modes (ntb, pb2 or TPAA, see Figure 9) have been reported to be SOD mimics. However, it has been shown that the superoxide anion will not reduce FeIII(salen) complexes at a rate fast enough for them to be competent SOD catalysts.

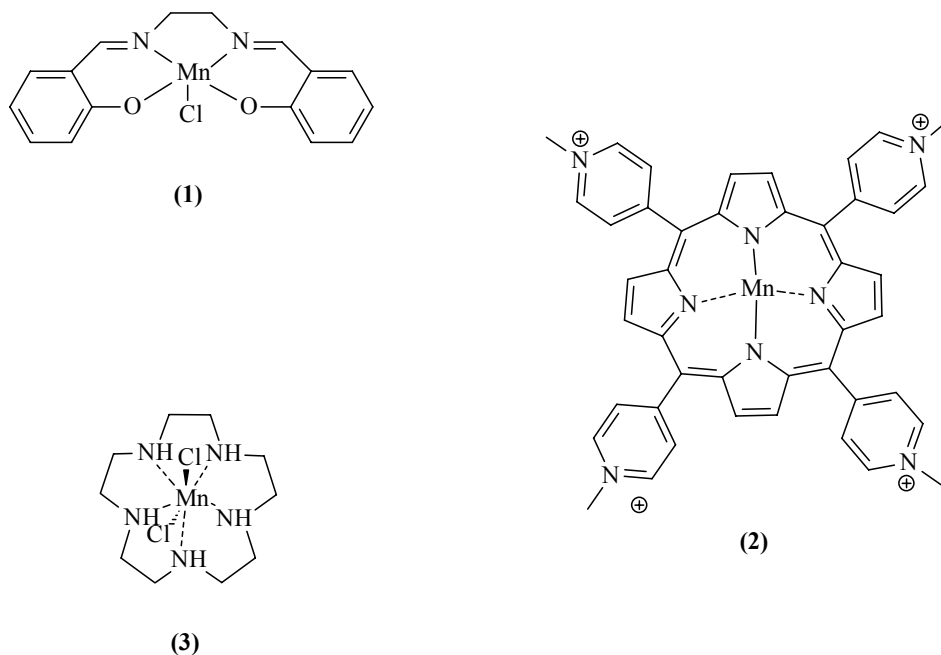


Figure 8. Representative examples of Mn(III)SOD functional mimic classes, (1) salen, (2) porphyrin and (3) pentaazacyclopentadecane complexes.

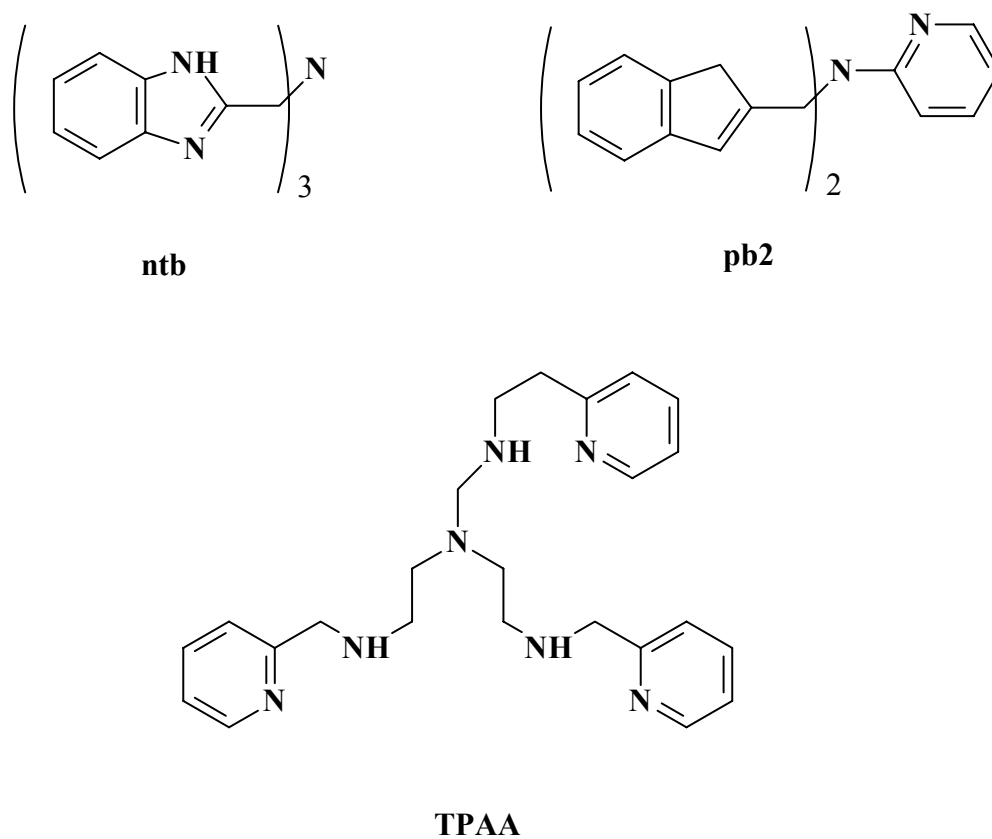


Figure 9. Ligands for effective FeSOD mimicking complexes.

Although the search for complexes effectively catalyzing the dismutation of the superoxide ion has not stopped [46-61], new ligands outside the above-described classes rarely appear. Let me list some of the novel yet conventional ligands (conventional in the sense that they try to copy some important features of the enzymatic active sites). One of them is a ligand designed to accurately model the active site of the Fe(III)SOD enzyme [62]. It is an N_3O tripodal tetradentate ligand: bis(6-pivalamido-2-pyridylmethyl) carboxymethylamine (bpga) (Figure 10) and the structural model is $[Fe(bpga)N_3(OCH_3)]$, i.e. an azide inhibited Fe(III)SOD enzyme mimic. Other molecules are the tridentate bis(1-methylimidazol-2-yl)-(4-methoxyphen-1-yl)methanol (Hbmimp) (Figure 10) and bis[(1-methylimidazol-2-yl)](2-aminophenyl)methanol (Hbmiapm) and the active site mimicking manganese complexes are $[MnII(Hbmimp)_2(NO_3)](NO_3).Et_2O$, $[MnIII(bmimp)_2(OAc)].2CH_2Cl_2$, and $[MnIII(bmiapm)_2(OAc)].MeOH.H_2O.CH_2Cl_2$ (3) containing the new ligands [63]. Still another is a novel acyclic, rigid pentadentate chelate, 2,6-diacetylpyridinebis(semioxamazine) [$H_2dapsox$] that is [43]. The Mn(II) and Fe(III) complexes of this ligand showed high SOD activities despite the rigidity of the ligand (Figure 10). The manganese(III) complexes based on tridentate ligands bearing imidazole and phenol moieties (pi, phim, phiim) (Figure 10) also actively catalysed the dismutation of the superoxide ion [64].

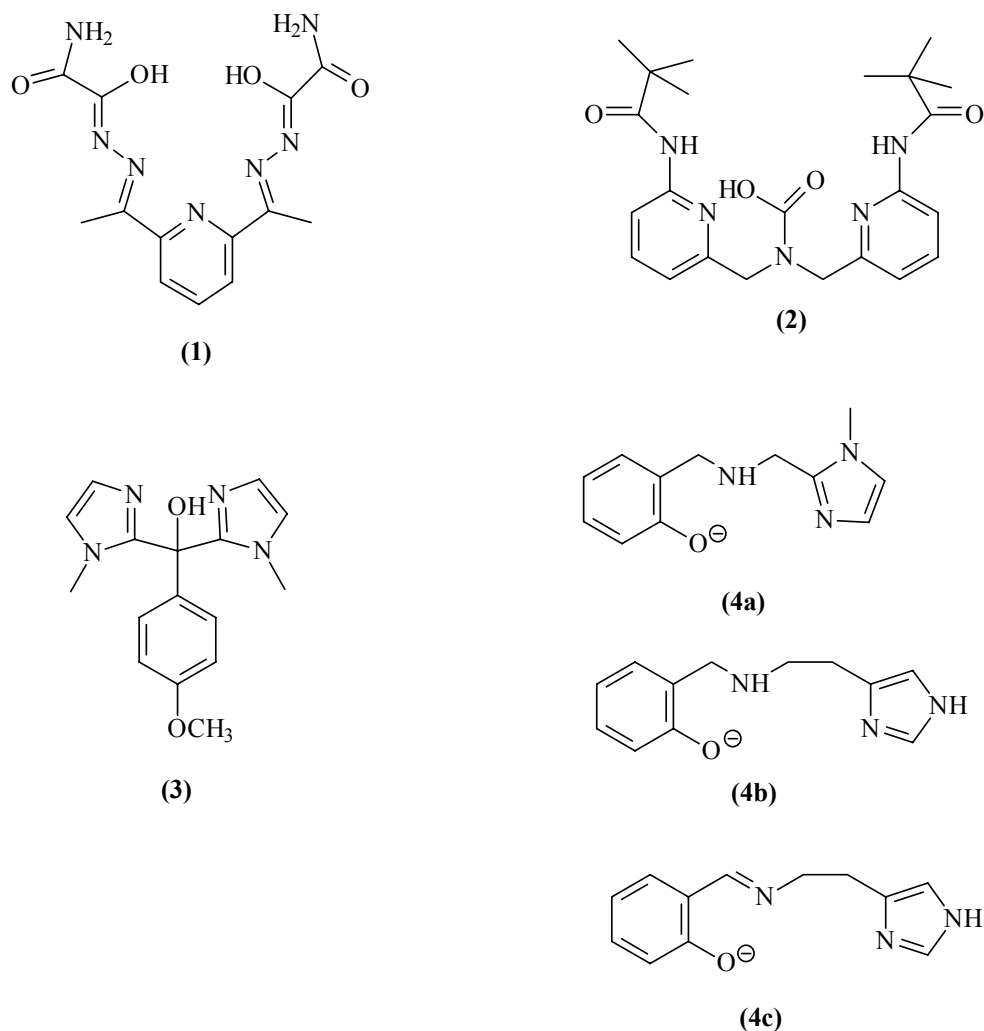


Figure 10. Ligands for effective FeSOD and MnSOD mimicking complexes (1) H₂dapsox, (2) bpga, (3) Hbmipm, (4a-c) pi, phim, phiim (for full names, see text).

The manganese complex was more active, however, the higher stability of the iron complex over a very wide pH range may be advantageous in possible applications.

Some ligands that do not copy nearly any feature of the enzymatic active sites have also been tried and the obtained complexes displayed SOD activities. Iron–flavonoid complexes [(–)-epicatechin, luteolin] [65] were active in dismutating the superoxide ion. Curcumin and its certain derivatives applied for preparing manganese complexes which also proved to be potent SOD enzyme mimics [66].

Finally, let me mention that FeCl₃ in acetonitrile was found to be very effective in the superoxide dismutase reaction [67].

Cu,ZnSOD Enzyme Mimics

Many binuclear and mononuclear complexes having certain level of SOD activity have been prepared. The binuclear complexes relate to the active site of Cu,ZnSOD enzymes the better, however, it turned out that the presence of the copper ion is only crucial as far as SOD activity is concerned. There is SOD activity either the Zn(II) ion is replaced by some other ions or there is no other ion at all in the complex, i.e. we are having monometallic copper complex of some kind. In the followings, first the Cu–Zn mimics, then, the Cu–other metal ion complexes and finally, the mononuclear copper complexes displaying SOD activities are reviewed. This sequence applies for both the structural and the functional models.

Structural Mimics

The obvious, albeit not necessarily easy way of structural modelling would be the preparation of Cu,Zn complexes having the amino acids as ligands that are found in the active site of the enzyme in the immediate vicinity of the metal ions. It is not easy, since the controlled and reproducible synthesis of heterobinuclear complexes with mixed amino acid ligands would be needed. I could not locate work of this type. Another approach is trying to prepare Cu,Zn heterobinuclear complexes with histidine as ligands, since it is the amino acid, which is the most significant in the active site of the enzyme. I could not find work of this type either. Yet another approach is having any kind of amino acids or short peptides as ligands, but insisting in an imidazolate bridge between the two metal ions (this bridge may come from any imidazole-containing derivative). Even relaxing the criteria of being functional mimetic in the strict sense (exactly the same amino acids in the same positions as in the active sites) afforded only few hits: Na[(glygly)Cu–im–Zn(glygly)] (H₂glygly is glycylglycine and imH is imidazole) [68], Na[(glyala)Cu–im–X(glyala)] [H₂glyala is glycylalanine, X is either Zn(II) or Cu(II)] [69], Na[(Salala)Cu–im–X(Salala)] [Salala is salicyldehenalinate, X is Zn(II), Cu(II) or Ni(II)] [70] complexes with SOD activities have been prepared.

Even if mononuclear copper complexes with amino acid or peptide ligands are also included in the group (the complexes must have SOD activity though), the number does not go up tremendously. The complexes are as follows: [SalalaCu(II)–OH₂] [70], [SalalaCu(II)–im] [70], [Cu(II)dipeptide].nH₂O (dipeptides are L-alanine-L-isoleucine, L-alanine-L-threonine and L-alanine-L-tyrosine) [71], bis[cyclo(histidylhistidine)]Cu(II) [72] Cu(II)-[histidine]₂ [73, 74], Cu(II) complexes of Ac-hisvalhis-NH₂ and Ac-hisvalglyasp-NH₂ [75], Cu(II) complexes of polyaminocarboxylates prepared from ethylene diamine tetraacetate (EDTA) conjugated to tyrosine and phenylalanine [76] (for the ligands, see Figure 11).

There are some theoretical works mainly concerning the mechanism of the dismutation reaction by the enzyme. They use a more complete model (both ions and their immediate surroundings or even more are included) [77] or a(n) (over)simplified approach (only the copper ion and histidine ligands are involved) [78]. They give some insight into the geometric arrangement of the active site.

Many types of copper-amino acid and copper-peptide complexes (either mono-, bi- or trinuclear) have been prepared since long (for a review, see e.g. [79]), however, they either do not have SOD activity or they were not tested in the dismutation reaction of the superoxide radical ion, therefore, they are not included in this review.

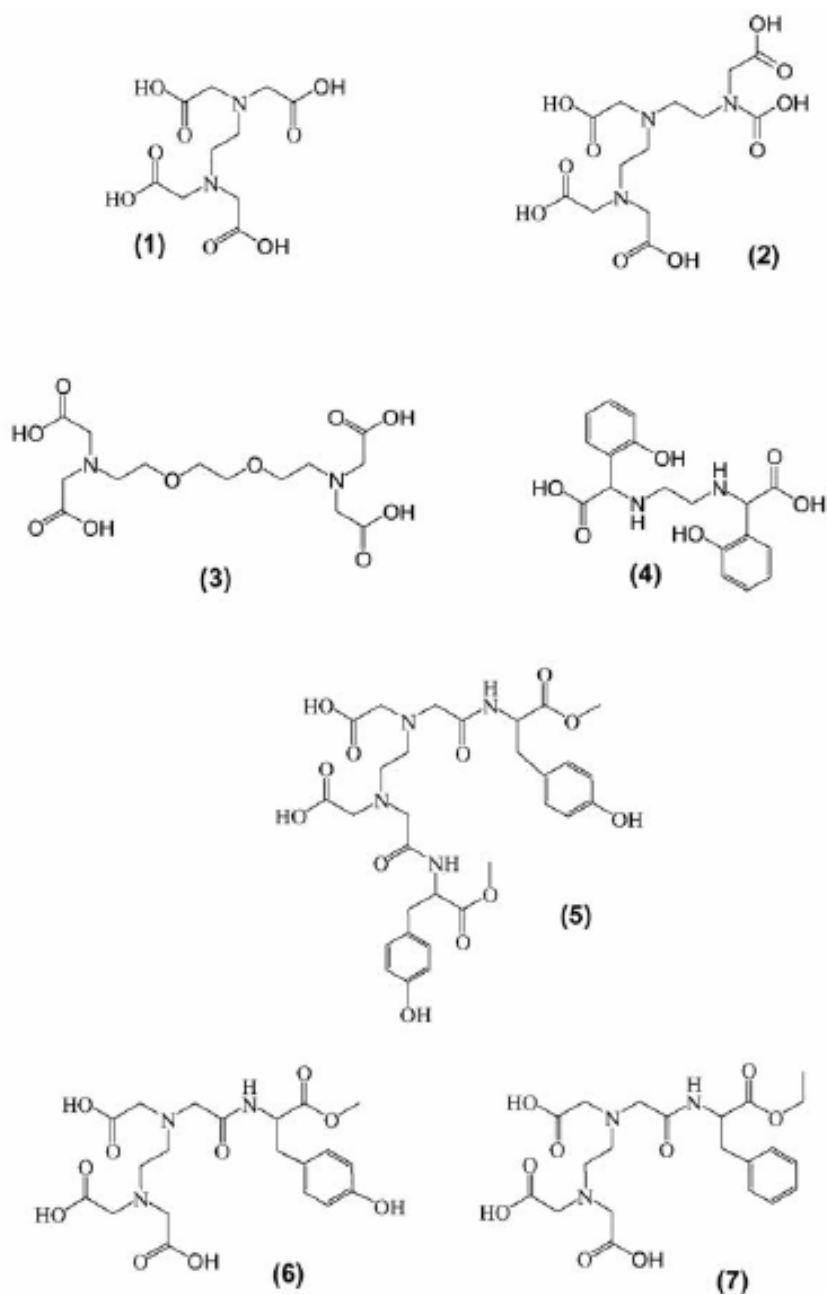


Figure 11 Polyaminocarboxylic acids and derivatives (1)-(7) – ligands for preparing Cu(II) complexes with SOD activities.

Functional Mimics

Most functional mimics bear some resemblance (the larger is the similarity the better) to the immediate surroundings of the metal ions. These ligand types mostly form chelates around the Cu(II) and the Zn(II) ions [or the ions substituting this latter: Cu(II), Ni(II)] and there is imidazolate bridge between the ions, i.e. one coordinating nitrogen is given by the

bridge to each ion. The ligands were tridentate (diethylenetriamine (dien) [80-82], pentamethyldiethylenetriamine (pmdt) [83]) or tetradentate (tris(2-aminoethyl)amine (trien) [84]) or their mixture [85] (Figure 12). Other tri- and tetradentate ions were also used in preparing Cu–O₂ complexes used for mimicking copper-containing enzymes (other than the Cu,ZnSOD enzyme) as summarised in a review [86].

Some novel ligands were also designed and synthesised having enough coordination sites in one single molecule to be able to coordinate to two metal ions providing either exactly the coordinating atoms that are found in the active site Cu,ZnSOD enzyme [87] (Figure 13), or closely resembling them [88-91].

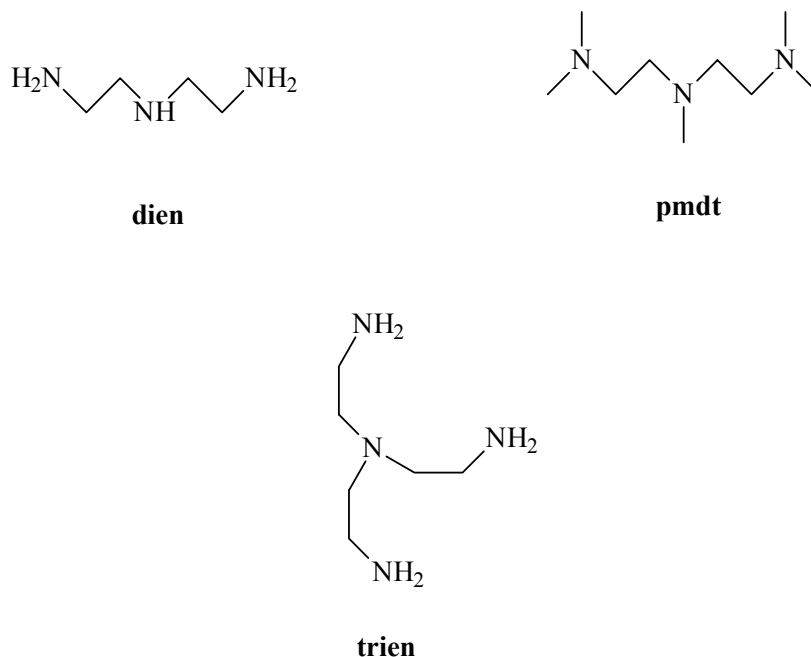


Figure 12. Tridentate (dien, pmdt) and tetradentate (pmdt) ligands used for preparing Cu(II)-containing SOD enzyme mimicking complexes.

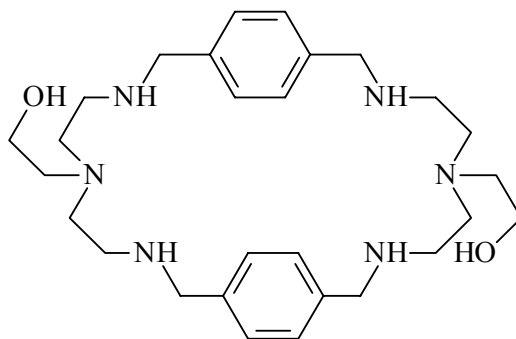


Figure 13. A macrocyclic compound (3,6,9,16,19,22-hexaaza-6,19-bis(2-hydroxyethyl)tricyclo[22,2,2,211,14]triaconta-1,11,13,24,27,29-hexaene), capable to act as a single ligand in homo- or heterobinuclear metal complexes.

There are some works where the bridge was not imidazolate but either ethylenediamine [92] or oxalate [93] and the Cu,Zn complexes still displayed SOD activities. Binuclear copper complexes with SOD activities were prepared with ligands containing a tetrathioether-tetraamino moiety [94], where the bridge between the metal ions is C or C=C. Pyridazolate-bridged dicopper complexes with SOD activities have been made too [95].

Works exist where there is no bridge at all, but one (*N,N',N'',N'''*-tetra(2-aminoethyl)-1,1,2,2-ethanetetraamide [96]), two large molecules (tolfenamic acids [97]) couple the two metal ions (two Cu(II) ions in these cases) providing nearly enough coordinating atoms for full coordination. The empty coordination sites (if such sites remain) are filled with small molecules like water or *N,N*-dimethylformamide [97].

It is known that mononuclear copper complexes may also have SOD activities (for a recent review, see [98]). Indeed, not only the presence of the second metal ion is not an absolute requirement, but the coordination environment does not have to resemble rigorously to that of the metal ions in the enzyme. Various macrocyclic ligands can coordinate to the Cu(II) ion through the combination of nitrogen and oxygen atoms [99]. Sulfonamide derivatives served as ligands in Cu(II) complexes as well, displaying SOD activities [100-102]. Cimetidine [103], a substituted benzotriazole [104], various imidazole derivatives [82, 100, 105, 106], diethylenetriamine (dien) [82, 106], diethylenetriamine (tren) derivatives [105, 107, 108], phenantroline [109], β -cyclodextrin-homocarnosine conjugates [110], (salicylideneimino)benzo-15-crown-5 [111], curcumin, (a conjugated polyphenol with 1,3 dioxo motif) [112], polypyridylamines [113], mono- and bis-thiosemicarbazones [114] also served as ligands in SOD active mononuclear copper complexes. The copper complexes with N_4 ligands {like *N,N'*-bis(2-pyridylmethylene)-1,4-butanediamine [115] and *N,N'*-bis(2-pyridyl-phenyl)methylene-1,4-butanediamine [115], *N,N'*-bis(2-(6-methylpyridyl)methylene)-1,4-butanediamine [116], *N,N'*-propylenebis(2-actoylpyridineiminate) [117], 1,8-bis(2-pyridyl)-2,7-diazaoctadiene-1,7 [118], benzylbisthiosemicarbazone and 3,4,10,11-tetraphenyl-1,2,5,8,9,12,13-octaazacyclotetradeca-7,14-dithione-2,4,9,11-tetraene [119], *N,N'*-bis-(1-pyridin-2-yl-ethylidene)-propane-1,3-diamine [120] – all are Schiff bases, 6-(9-fluorenyl)-1,4,8,11-tetraazaandecane-5,7-dione [121]}, 2-amino-*N*-(2-oxo-2-(2-(pyridin-2-yl)ethylamino)ethyl)acetamide [122], a mix of ligands (carboxylate, benzimidazole, 1,10-phenanthroline and bipyridine) [123] and cyanoguanidine (cnge) and o-phenanthroline [124] are proved to have SOD activity.

MISCELLANEOUS

Mimics of the major types of SOD enzymes encompass the vast majority of the relevant original and review papers. However, studies can be found concerning the active site mimicking complexes for the NiSOD enzyme and there are, although sporadic but existing reports on the SOD activities of metal complexes not having enzyme counterparts.

The synthesis and structural properties of a nickel complex with the hydrotris[thioxotriazolyl-3-(2-pyridyl)]borate has been reported [125]. The coordination mode bears some resemblance to the active site of NiSOD, although the SOD activity of the complex was not tested. The metal ion is present in a slightly distorted octahedral geometry (N_4S_2 coordination) bound by two ligands that behave in the S,N/N' coordination mode: one

of the three arms of each tripod is bound to the metal ion with the thioxo group, the second chelates N/N' with the triazoline and pyridine nitrogen atoms and the third does not participate in the metal coordination.

Mono- and binuclear Ni(II) complexes with tetradentate N(amine)₂S(thiolate)₂ ligation have been prepared as well [126]. The ligands were as follows: (R,R)-*N,N'*-bis(1-carboxy-2-mercaptoethyl)-1,2-diaminoethane, *N,N'*-bis(2-methyl-2-mercapto-prop-1-yl)-1,3-diamino-2,2-dimethylpropane or rac-*N,N'*-bis(2-mercapto-2-methyl-prop-1-yl)-1,3-cyclohexane-diamine. The complexes were intended as models for Ni-containing metalloenzymes. They are hoped to be good SOD mimics, although they have not been tested in the dismutation reaction of the superoxide radical anion as yet. As far as the coordination environment is concerned, these complexes should be better SOD enzyme functional mimics than the previous one. Search for good structural mimetics still goes on and, hopefully it is helped by gathering more details about the structure of the active site and its surroundings [127].

Bis-quinoline-bis-mercaptocobalt(II) was the first SOD active mononuclear cobalt complex [128]. The complex is tetrahedral with nitrogen donor atoms from the two quinoline ligands and sulphur donor atoms from the two mercapto groups (N₂S₂ attachment to the central ion). SOD activity could also be observed with two Co(II)-sugar complexes (the ligands were 3,4,6-tri-*O*-(2-picolyl)-1,2-*O*-ethylidene- α -D-galactopyranose and 3,4,6-tri-*O*-(2-picolyl)-D-galactal [129] (Figure 14)), where the metal environments were N₃O₃ octahedral with 3 pyridines and 3 ether groups from the sugar moiety.

Synthesis, characterisation and SOD activities of some ruthenium(III)-oxime complexes have also been reported some time ago [130].

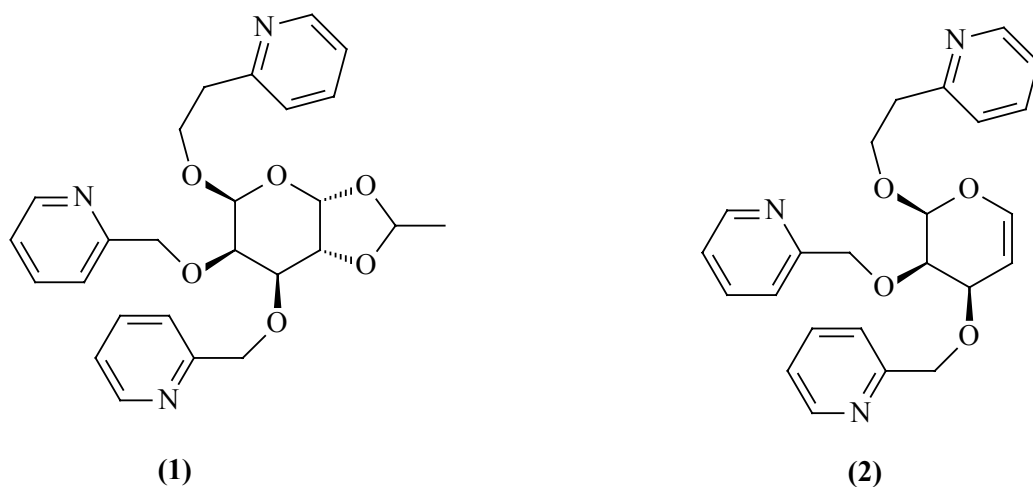


Figure 14. Sugar derivative as ligands for Co(II) complexes with SOD activities [(1) 3,4,6-tri-*O*-(2-picolyl)-1,2-*O*-ethylidene- α -D-galactopyranose and (2) 3,4,6-tri-*O*-(2-picolyl)-D-galactal].

SUPPORTED COMPLEXES MIMICKING THE ACTIVE SITES OF SOD ENZYMES

Complexes attached or enclosed to or in solid materials can have many applications. Let me mention only the perhaps most obvious one: complexes on or in solid surfaces can act as heterogeneous catalysts (see, e.g. a recent review [131]), and the immobilised biocomplexes are often called bioinspired catalysts (e.g. [132]).

SOD enzymes or SOD-mimicking complexes (where SOD activity is demonstrated) were not too often grafted onto solid or semisolid substances. The enzymes when they are deposited onto solids (bonded to electrodes) are used as biosensors [133, 134]. The immobilised SOD-mimicking complexes offer the possibility of using them as selective oxygen transfer catalysts in “real-life” chemistry, i.e. under higher temperatures than the physiological, higher pressures than atmospheric and in a variety of solvents.

Since the number of papers dealing with surface-grafted SOD-mimicking complexes is small, this chapter will not be divided into subchapters.

An imidazolate-bridged Cu(II)–Zn(II) complex (Cu(II)-diethylene-triamino- μ -imidazolato-Zn(II)-tris(aminoethyl)amine perchlorate) and their mononuclear substructure complexes containing the Cu(II) ion were immobilised in MCM-41 and among the layers of montmorillonite by adsorption (attachment occurred mainly through hydrogen bonding) or ion exchange [135], onto the surface of silica gel by either adsorption (mainly through hydrogen bonding) [106] or covalent grafting [136]. The SOD activity of the complexes were measured and it was found that they were all active, however, the most active catalyst was the binuclear complex when surface grafting occurred *via* adsorbing it onto silica gel. The activity approached that of the native Cu,ZnSOD enzyme.

Mononuclear, covalently grafted Cu(II)–amino acid (L-histidine, C- or N-protected L-histidine) complexes were also prepared using Merrifield’s resin as support [137, 138]. The flexible support (polystyrene-co-vinylbenzyl chloride-co-divinyl-benzene) was thought to contribute to enhanced SOD activity through helping to assume an optimum conformation for the active site. It was observed that the SOD activity was considerably, with more than an order of magnitude higher when the protected amino acids were the ligands and not the unprotected histidine. The best activity came relatively close to that of the native Cu,ZnSOD enzyme.

Mononuclear Cu(II)–L-tyrosine methylester and Cu(II)–Boc-L-tyrosine complexes were built onto chloropropylated silica gel [139] by covalent grafting of the protected amino acids, then, allowing complexation either without or with excess of the protected amino acids. By varying the solvent of synthesis and the availability of the amino acid derivatives the SOD activities of the supported complexes could be severely influenced. The activities were higher when ligands were available for complexation in excess, and they were the highest when isopropanol was chosen as the solvent of preparation.

Polymer-supported Mn(II)-, Cu(II)-, Fe(III)- and Co(II)-containing catalysts with SOD activities have been prepared by using 1-vinylimidazole or 4-vinylimidazole and ethyleneglycol dimethylacrylate as monomers [140]. Polymerisation occurred in the presence of the appropriate metal ions. SOD activity was found to be higher when 1-vinylimidazole was one of the starting monomer and it decreased in the following order Mn(II) > Co(II) > Cu(II) > Fe(III).

As it seen from above, works for preparing durable supported catalysts with dismutation capabilities have already provided promising results. In the near future these catalysts should be tried under conditions generally used in bench synthetic chemistry and in fine chemical industrial synthesis.

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